REMARKS

These remarks and the above amendments are responsive to the Office Action dated April 2, 2003. Claims 36-57 are pending in the application. In the Office Action, the Examiner rejected claims 36-57 under 35 U.S.C. § 112, first paragraph, as nonenabled (claims 36-57), or second paragraph, as indefinite (claims 36 and 48). Significantly, none of the claims was rejected in view of prior art. Applicants traverse the rejections, contending that the claims are enabled and definite as submitted. Nevertheless, to expedite issuance of a patent, and to more particularly point out and distinctly claim aspects of the invention, applicants have amended claims 36, 49, and 50, and added new claim 58. Applicants believe that the amendment to claim 36 renders moot the rejections under 35 U.S.C. § 112. Therefore, in view of that amendment and the following remarks, applicants respectfully request reconsideration of the application and the prompt issuance of a Notice of Allowance.

I. Information Disclosure Statement

The Examiner objected to a Japanese document (4-344464) submitted in the Information Disclosure Statement filed May 8, 2002 as not being in the English language. The Examiner apparently placed the reference in the application file, without considering the reference as to the merits. In response, applicants apologize for any confusion, and thank the Examiner for his attentive review of the disclosed references. Applicants do not have an English translation of the Japanese reference.

II. Drawings

The Examiner objected to Figures 7, 8, and 9. Specifically, the Examiner stated that these figures have "two components" each and thus "should contain reference to

each individual component of the figures." Applicants traverse these rejections, contending that the references to these drawings in the specification were clear as filed. Nevertheless, to expedite allowance, applicants have followed the Examiner's suggestion and amended the legends for Figures 7, 8, and 9 in the "Brief Description of the Drawings" so that they more closely resemble in format the legend for Figure 4 on page 14 of the specification. Applicants do not believe that the drawings for Figures 7, 8, or 9 require amendment, because each already included separate designators for panels A and B. However, if the Examiner disagrees, or if the Examiner has any additional questions or comments regarding the drawings, the Examiner is invited to contact applicants' undersigned attorney at the telephone number indicated below.

III. Claim Rejections – 35 U.S.C. § 112

The Examiner rejected claims 36-57 under 35 U.S.C. § 112, first paragraph, as nonenabled (claims 36-57), or second paragraph, as indefinite (claims 36 and 48). Significantly, none of the claims was rejected in view of prior art. Applicants traverse the rejections, contending that the claims are enabled and definite as submitted. Nevertheless, to expedite issuance of a patent, and to more particularly point out and distinctly claim aspects of the invention, applicants have amended claims 36, 49, and 50, and added new claim 58. Applicants believe that the amendment to claim 36 (adding --in vitro--) renders moot the rejections under 35 U.S.C. § 112. Therefore, in view of that amendment and the following remarks, applicants respectfully request reconsideration of the application and the prompt issuance of a Notice of Allowance.

A. Claims 36-57

The Examiner rejected claims 36-57 under 35 U.S.C. § 112, first paragraph. More specifically, the Examiner stated "the specification does not enable any person skilled in the art . . . to make or use the invention commensurate in scope with these claims." Office action, paragraph 5. The discussion of these rejections is several pages long. However, in brief, the Examiner appears to have two concerns: (1) that the specification allegedly does not enable the in vivo application of the claimed methods (Office action, paragraphs 5-13), and (2) that the use of the claimed invention, in its full scope, allegedly would require undue experimentation, because the claims cover many types of reactions (Office action, paragraph 14). Applicants disagree with both assertions. In particular, applicants believe that the claimed methods are suitable for use both in vitro and in vivo. Moreover, applicants also believe that use of the claimed methods would not require undue experimentation; indeed, applicants carefully enabled that use with detailed listings of assay components, instrument settings, and the like, for a variety of assays, with actual experimental data showing its efficacy. Nevertheless, to expedite issuance of a patent, applicants have amended the claims to focus on in vitro use, which the Examiner has admitted are enabled, reserving their right to pursue the unamended claims to in vitro and in vivo use in continuation applications.

1. Nonenablement (OA, paragraphs 6-13)

The Examiner objected to claims 36-57 as covering both in vitro and in vivo methods, while allegedly enabling only in vitro methods. Specifically, while admitting that the specification is enabling for "an *in vitro* method of measuring the generation or consumption of cAMP and cGMP by adenylyl cyclase and G-proteins respectively in the

presence and absence of test compounds," the Examiner asserted that the specification "does not reasonably provide enablement for any other enzymes which may consume or generate cyclic nucleotides or other natural or non-naturally occurring cyclic nucleotides or the performance of the assay *in vivo*." Office action, paragraph 5.

Applicants agree with the Examiner's conclusion that the application is enabling for in vitro methods. However, they disagree with the Examiner's statement that this enablement is limited to cAMP, cGMP, adenylyl cyclase, and G-proteins. Instead, applicants believe that the application is enabling with respect to any cyclic nucleotide, and any enzyme that generates or consumes a cyclic nucleotide, in vitro or in vivo.

The claimed methods involve (1) conducting a reaction that generates or consumes a cyclic nucleotide in the presence of a candidate compound, (2) contacting a product of the reaction with a luminescent tracer and with the opposite member of a specific binding pair to the cyclic nucleotide, (3) illuminating the tracer with polarized light, (4) detecting the extent of polarization of light emitted from the tracer, and (5) identifying the candidate compound as a modulator of the reaction based on the extent of polarization of the emitted light.

The claimed methods involve "the opposite member of a specific binding pair to the cyclic nucleotide." However, a person of ordinary skill in the art easily could generate this member for any cyclic nucleotide, not just cAMP or cGMP, using standard techniques, for example, by producing polyclonal or monoclonal antibodies.

The claimed methods do <u>not</u> involve or require knowledge of the enzyme or other agent that consumes or generates the cyclic nucleotide. Instead, the claimed methods simply require that such an enzyme or agent exists, so that the effects, if any,

of the candidate compound on the reaction mediated by the enzyme or other agent can be assessed. Thus, a person of ordinary skill in the art could perform the assay based on disclosure in the application for any enzyme or agent that generates or consumes a cyclic nucleotide, not just adenylyl cyclase, guanylyl cyclase, phosphodiesterase, or G-proteins.

The claimed methods may be performed in vitro or in vivo. The methods may be performed in vitro by introducing suitable reaction components into a suitable container, including microplate wells. The suitable reaction components may include isolated enzyme, such as adenylyl cyclase or guanylyl cyclase or phosphodiesterase, among others. See, e.g., Application, Example 3, pages 26-33. The suitable reaction components also may include lysates from whole cells that contain a suitable enzyme or other agent. See, e.g., Application, Example 8, pages 34-38. (Applicants added new claim 58, supported by Example 8, among others, to point out that reaction products may arise from cell lysates.) The methods may be performed in vivo by introducing suitable assay components (such as the luminescent tracer and/or member of the binding pair) into a cell, or a component thereof, using standard techniques, such as microinjection.

In summary, applicants believe that the claimed methods may be used, in vitro or in vivo, for any cyclic nucleotide and for any enzyme or other agent capable of generating or consuming a cyclic nucleotide. Moreover, applicants believe that such use is fully enabled. Nevertheless, to expedite issuance of a patent, applicants have amended claim 36 to focus on in vitro methods, where the product of a reaction that generates or consumes a cyclic nucleotide is contacted, in vitro, with a luminescent

tracer and with the opposite member of a specific binding pair. Consequently, the Examiner's arguments regarding in vivo methods are moot, and the associated rejections should be withdrawn. Applicants reserve, among others, their right to pursue claims directed to in vitro and in vivo methods in continuation applications.

2. Undue Experimentation (OA, paragraph 14)

The Examiner also objected to claims 36-57 as requiring undue experimentation. Applicants disagree. In particular, the claimed methods may be practiced essentially without prefatory experimentation using the detailed information provided in the application regarding exemplary assay components, exemplary assay conditions (e.g., pH, salt concentration, etc.), and exemplary detection methods, among others. Moreover, as discussed above, although the examples described in the application deal primarily with the cyclic nucleotides cAMP and cGMP, and with the enzymes adenylyl cyclase, guanylyl cyclase, phosphodiesterase, and G-proteins, a person of ordinary skill in the art easily could apply the methods to other cyclic nucleotides and other enzymes or agents that generate or consume cyclic nucleotides, without undue experimentation, simply by providing a luminescent tracer (that can simply be a luminescently labeled version of the cyclic nucleotide, among others) and the opposite member of a specific binding pair to the cyclic nucleotide (that can simply be an antibody, among others).

Applicants admit that there are many reactions that generate or consume cyclic nucleotides. Nevertheless, applicants' claims should not be limited only to cyclic nucleotides, enzymes, and modulators expressly identified or shown in an example in the application. Applicants are not claiming the cyclic nucleotides themselves, or the enzymes that generate or consume the cyclic nucleotides, or the candidate compounds

that modulate the enzymes that generate or consume the cyclic nucleotides. Applicants also are not claiming methods of synthesizing such moieties. Instead, applicants presently are claiming methods of identifying compounds as modulators of reactions that generate or consume cyclic nucleotides. It is not necessary to identify every cyclic nucleotide or enzyme or modulator that may be used in the claimed methods to enable those methods or to permit their practice without undue experimentation. Indeed, a preferred use of the claimed methods is to identify previously unknown modulators of cyclic nucleotide reactions from libraries of candidate compounds in the search for new drugs.

The Examiner states that there is an "absence of working examples" in the application directed to known modulators of reactions that generate or consume cyclic nucleotides. Office action, paragraph 14, page 7, lines 3-4. Applicants disagree. The specification provides specific working examples of a general method of identifying whether candidate compounds (such as forskolin, isoproterenol and propranolol) are modulators of known reactions (utilizing the enzymes adenylyl cyclase and/or guanylyl cyclase) that generate or consume cyclic nucleotides (such as cAMP and cGMP). See, e.g., Application, Examples 3 and 8, for methods, and Figures 10-13, for data, among others. These working examples demonstrate the utility of the method for identifying modulators of reactions that employ very different enzymatic mechanisms to generate or consume their respective cyclic nucleotides. Thus, a person of ordinary skill in the art could utilize methods disclosed and claimed in the application to identify whether a particular candidate compound is a modulator of reactions that generate or consume cyclic nucleotides, without undue experimentation.

In summary, applicants believe that the application does enable a person of ordinary skill in the art to make or use the invention commensurate with the scope of the claims. Thus, applicants respectfully request withdrawal of the rejection.

B. Claims 36 and 48

The Examiner rejected claims 36 and 48 under 35 U.S.C. § 112, second paragraph, as being indefinite. In particular, the Examiner stated that the "term 'modulator' is a relative term which renders the claim indefinite." Office action, p. 7, paragraph 16. The Examiner further stated that "[t]he term 'modulator' is not defined by the claim, the specification does not provide a standard for ascertaining the requisite degree, and one of ordinary skill in the art would not be reasonably appraised of the scope of the invention." Id. Applicants traverse these rejections. In particular, applicants believe that the term "modulator" is defined, that the specification does provide suitable standards for ascertaining the degree of modulation (even though such an ascertainment is not required by the claims), and that those of ordinary skill in the art would be reasonably apprised of the scope of the invention.

The rejected claims are directed to methods of "identifying a compound as a modulator of a reaction that generates or consumes a cyclic nucleotide." In this context, and in agreement with its plain meaning, a "modulator" may be any compound or other agent capable of modulating (e.g., influencing or affecting) the indicated reaction. The specification states:

> [A] modulator generally comprises any compound or other species capable of modulating the activity of receptors, enzymes, and/or other species involved in the generation of analyte. The modulator may be an agonist or an inhibitor of analyte production, meaning that it may promote or inhibit analyte production. For example, in a cyclic nucleotide assay,

preferred agonists include forskolin and isoproterenol, and preferred inhibitors include propranolol.

Application, page 24, lines 8-13.

The term "modulator" is defined broadly. Modulators may be natural or synthetic compounds. For example, as the Examiner acknowledges, they may be "growth factors, neurotransmitters, releasing factors, or circulating hormones," and they "may inhibit, increase, decrease, or bind to the enzyme involved in the reaction." Modulators also may be currently known or currently unknown. The claimed methods provide mechanisms for "identifying" modulators, whether natural or synthetic, and whether known or unknown. Thus, without limitation, the claimed methods are particularly suitable for drug screening, in which libraries of candidate modulators are screened for an ability to modulate a reaction that generates or consumes a cyclic nucleotide. The claimed methods are flexible: they do not require looking at the modulator itself, but rather for the effects of the modulator on a rate or amount or other indicator of cyclic nucleotide generation or consumption.

The rejected claims are directed to methods of "identifying" modulators, without requiring a determination of the degree to which reactions are modulated. Thus, a modulator may simply be identified by a "low" extent of polarization or a "high" extent of polarization, depending on the reaction. Nevertheless, the claimed methods may be suitable for ascertaining degrees, to the extent such an ascertainment is interesting or desirable. For example, an exemplary method of determining the degree to which a candidate compound affects the activity of a reaction (and is therefore a modulator) is to compare the activity of the reaction in the absence of the candidate compound to the

activity of the reaction in the presence of the candidate compound, for example, as recited in claim 48, and further developed in claims 49 and 50.

In summary, applicants believe that the term "modulator" is definite, and therefore that the rejection of claims 36 and 48 as indefinite should be withdrawn.

The scope of the pending claims would be reasonably apprised by one of ordinary skill in the art. In particular, one of ordinary skill would understand that the claims cover methods of identifying a compound as a modulator of a reaction that generates or consumes a cyclic nucleotide, where the candidate compound is arbitrary, but where the steps for performing the method are as recited, including conducting, contacting, illuminating, measuring, and identifying.

Applicants believe that this application is in condition for allowance, in view of the above amendments and remarks. Accordingly, applicants respectfully request that the Examiner issue a Notice of Allowance covering the claims. If the Examiner has any questions, or if a telephone interview would in any way advance prosecution of the application, please contact the undersigned attorney of record.

CERTIFICATE OF MAILING

I hereby certify that this correspondence is being deposited with the United States Postal Service as first class mail in an envelope addressed to: Commissioner for Patents, P.O. Box 1450, Alexandria, Virginia 22313-1450 on October 2, 2003.

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Respectfully submitted,

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